REMARKS

In the present Amendment, the specification has been amended to add a missing sentence at page 38, line 10 that was inadvertently omitted from the translation of the Japanese specification of the international application (WO 2005/000312 A1), as shown in the attached sheets. Claim 19 has been amended to add a period at the end. Claim 21 has been amended to recite "applying a fine powder by fusion coating using an agitation method to core particles." Support for the amendment is found, for example, on page 38, lines 6 and 19-27, and in Test Example 5 and Fig. 5 of the specification. Claims 25 and 26 have been amended to add a comma "," after "claim 21." New claim 33 has been added. Claim 33 is directed to the same medicament sustained release particles as those of claim 30 and support for claim 33 is found, for example, on page 25, lines 29-31, page 35, line 34 to page 36, line 1, and page 38, lines 6 and 19-27 of the specification. No new matter has been added, and entry of the Amendment is respectfully requested.

Upon entry of the Amendment, claims 1-33 will be pending, of which claims 1-20, 31 and 32 are withdrawn from consideration.

I. At page 3 of the Action, claims 21-25 and 27-30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Akiyama et al. (US 5,593,690) in view of Bartholomaeus et al. (US 2002/0176888).

Applicants submit that this rejection should be withdrawn because Akiyama et al. and Bartholomaeus et al. do not disclose or render obvious the present invention, either alone or in combination.

Present claim 21 as amended is directed to a method for preparing medicament sustained release particles comprising applying a fine powder by fusion coating using an agitation method

to core particles containing a pharmacologically active substance and a matrix base material that has a hydroxyl value of 60 or greater and contains a polyglycerol fatty acid ester. Present claim 30 relates to medicament sustained release particles obtainable by the method according to claim 21.

According to the method of the invention, the use of fusion coating performed by agitation enables the production of the desired fusion-coated particles in a high yield without having molten matter adhered on apparatus walls, unlike with fluid-bed fusion coating. See, page 55, lines 26-30 of the specification.

Furthermore, in the present invention, a matrix base material having a specific hydroxyl value is used. Therefore, when a fine powder is applied to core particles by fusion coating, the core particles are effectively prevented from electrostatically adhering to the inner walls of a mixer/granulator which may occur due to the matrix base material, enabling efficient production of a particulate pharmaceutical preparation having a sustained medicament release. See, page 56, lines 8-15 of the specification.

(a) Neither Akiyama et al. nor Bartholomaeus et al. teaches the "fusion coating" of the present invention

Akiyama et al. teaches a matrix preparation produced by dispersing a pharmaceutically active ingredient into a matrix that is solid at ambient temperature and composed of a fatty acid ester of a polyglycerol (abstract). However, as the Examiner acknowledged, Akiyama et al. does not teach "fusion-coating."

Bartholomaeus et al. teaches active-component controlled-release oral dosage formulations. Paragraphs [0040] and [0057] of Bartholomaeus et al. are cited by the Examiner. In paragraph [0040], Bartholomaeus et al. teaches that retarding coatings can be applied to the

dosage formulation by fusion processes or powder application processes; and in paragraph [0057], Bartholomaeus et al. teaches that wax coatings can be applied by fusion-coating in a fluidized bed and cooling after coating until completely hardened.

Citing these paragraphs, the Examiner concluded that Bartholomaeus et al. teaches the same "fusion coating" as in the present invention.

Applicants respectfully disagree.

The Examiner cited Muthiah (US 6,537,671), column 1, lines 30 to 35, in the footnote on page 6 of the Office Action. Based on Muthiah, the Examiner concluded on page 5, line 3 from the bottom, to page 6, line 2 of the Office Action that the fusion coating of Bartholomaeus et al. is "a method of applying a coating powder on a substrate in which dry, finely divided, free flowing heat fusible powders are deposited on the substrate and then fused and cured with heating, i.e., after coating, the coated substrate is subjected to a heat treatment, to form continuous or protective films."

However, the "fusion coating" of the present invention is a method comprising heating core particles so that a matrix base material becomes molten on the surface of the core particles, and fine powder present in the vicinity of the molten matrix base material adheres thereto; more specifically, a technique of forming a coating layer having fine particles on the surface of core particles by utilizing the adhesiveness of the molten matrix base material (see, for example, page 37, lines 3 to 12 of the specification).

That is, the material to be melted is different. Specifically, a powder deposited on a substrate is melted in Bartholomaeus et al. In contrast, a matrix base material is melted in the present invention, whereby fine powder adheres thereto to form a coating. Thus, the principles of these two methods are completely different. The "fusion coating" of the present invention is

clearly different from the fusion-coating process of Bartholomaeus et al. Therefore, Bartholomaeus et al. does not teach nor suggest the "fusion coating" of the present invention.

The Examiner stated on page 6, lines 5 to 9 of the Office Action that "[a]t the time of the invention, it would have been obvious to modify the methods of Akiyama et al. by utilizing the method of fusion coating of Bartholomaeus et al." However, as explained above, neither Akiyama et al. nor Bartholomaeus et al. teaches the fusion coating of the present invention. Therefore, the present invention is unobvious and is patentable over the combination of Akiyama et al. and Bartholomaeus et al.

(b) Neither Akiyama et al. nor Bartholomaeus et al. discloses "a matrix base material having a hydroxyl value of 60 or greater and containing a polyglycerol fatty acid ester"

The present inventors focused on the problem of electrostatic adhesion of core particles to the walls of a granulator that conventionally occurs due to the matrix base material during "fusion coating," as discussed above in Item (a); and inhibiting such electrostatic adhesion is one of the objects of the present invention. To achieve this object, the present invention utilizes a matrix substrate having a hydroxyl value of 60 or greater and containing a polyglycerol fatty acid ester, which is a characteristic feature of the present invention.

As the Examiner acknowledged on page 5, lines 13 to 14, and page 6, lines 3 to 4 of the Office Action, neither Akiyama et al. nor Bartholomaeus et al. teaches a matrix base material that has a hydroxyl value of 60 or greater and contains a polyglycerol fatty acid ester.

As discussed in Item (a) above, neither Akiyama et al. nor Bartholomaeus et al. teaches "fusion coating" of the present invention. Therefore, naturally, the problem of electrostatic adhesion of core particles cannot be addressed. Hence, there is no motivation to select a matrix

base material having a hydroxyl value of 60 or greater to prevent electrostatic adhesion of core particles.

Furthermore, the method of the present invention utilizes a matrix base material having a hydroxyl value of 60 or greater and containing a polyglycerol fatty acid ester, which inhibits adhesion of core particles to the wall surface of a granulator during fusion coating and enables efficient fusion coating. The Examiner will kindly refer to Examples 19 to 36, Comparative Example 17, and page 56, lines 8 to 15 of the specification. The fusion coating processes in Examples 19 to 36 (matrixes having a hydroxyl value of 60 or greater) show that no electrostatic adhesion of core particles occurred to give a product in good yield. In contrast, Comparative Example 17 (a matrix having a hydroxyl value of 15) shows that electrostatic adhesion of core particles occurred. This advantageous effect of the present invention cannot be expected from Akiyama et al. and Bartholomaeus et al.

(c) Neither Akiyama et al. nor Bartholomaeus et al. discloses "fusion coating using an agitation method (agitation granulation method)"

Another characteristic feature of the present invention is that the fusion coating is performed under agitation (using an agitating granulation method). Based on this feature, the present invention achieves the following remarkable effects: adhesion of core particles to the wall surface of a granulator during the fusion coating can be inhibited; fusion coating can be efficiently performed; and particles of a matrix formulation having a stably controlled medicament releasability can be obtained. The Examiner will kindly refer to page 38, lines 4 to 27, Test Example 5, and Figure 5 of the present application. For example, Figure 5 shows that particles fusion-coated by an agitation method have a remarkably improved drug elution control property, compared to particles fusion-coated by a fluidized bed method. That is, the particles

obtained by fusion coating using an agitation method have an excellent physical property (novel physical property) in terms of drug release control, compared to particles obtained by fusion coating using a fluidized bed method.

In contrast, Akiyama et al. does not teach "fusion coating." Bartholomaeus et al. does not teach the "fusion coating" of the present invention, either (see Item (a) above). Bartholomaeus et al. merely teaches fluidized bed coating in paragraphs [0057], [0071], [0080], [0088], [0096] and [0103]. Therefore, the superior effect of the particles obtained by fusion coating using an agitation method according to the present invention cannot be expected from Akiyama et al. and Bartholomaeus et al, either alone or in combination.

(d) Conclusion

As discussed above, the method of the present invention (claims 21-25 and 27-29) is unobvious and is patentable over Akiyama et al. and Bartholomaeus et al., either alone or in combination. The medicament sustained release particles obtained by the claimed method (claim 30) are also unobvious and are patentable over Akiyama et al. and Bartholomaeus et al., either alone or in combination.

In view of the above, reconsideration and withdrawal of the §103(a) rejection based on Akiyama et al. and Bartholomaeus et al. are respectfully requested.

II. At page 7 of the Action, claim 26 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Akiyama et al. and Bartholomaeus et al., and further in view of Kojima et al. (J. of Controlled Release, 2002).

Applicants submit that this rejection should be withdrawn for at least the same reasons that the § 103(a) rejection of claims 21-25 and 27-30 based on Akiyama et al. and Bartholomaeus et al. should be withdrawn, as discussed above. Kojima et al. is cited as teaching

that the release rate of theophylline was decreased by annealing at 80 °C for 4 h and that annealing of the matrix particle leads to alterations of the pellet structure and, consequently, of the release properties (page 339, 1st column, 1st full paragraph). Kojima et al. does not make up for the deficiencies of Akiyama et al. and Bartholomaeus et al.

Further, the present invention achieves another remarkable effect. In the present invention, the core particles may be subjected to a heat treatment prior to the fusion coating, as disclosed on page 39, line 1, to page 40, line 10, and in Test Example 4, and Figures 2 and 4 of the present specification. Crystalline transition of the matrix base material can be promoted by the heat treatment before the fusion coating, whereby stable drug release control properties can be maintained even after long-term storage. This effect cannot be expected from Akiyama et al., Bartholomaeus et al., or Kojima et al. Therefore, the method (Claim 26) of the present invention is unobvious and is patentable over Akiyama et al., Bartholomaeus et al., and Kojima et al., either alone or in combination.

New claim 33, directed to the same medicament sustained release particles as those of claim 30, is patentable over the cited references for at least the same reasons that claims 21-30 are patentable over the cited references, as discussed above.

Allowance is respectfully requested. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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WASHINGTON OFFICE
23373
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Date: September 21, 2010

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Yuso TOMOHIRA

Docket No: Q92094

Appln. No.: 10/561,444

Group Art Unit: 1612

Confirmation No.: 6406

Examiner: Darryl C SUTTON

Filed: December 20, 2005

For: MEDICAMENT SUSTAINED-RELEASE PARTICLES AND METHOD FOR PREPARING THE SAME

EXCESS CLAIM FEE PAYMENT LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

An Amendment Under 37 C.F.R. § 1.111 is attached hereto for concurrent filing in the above-identified application. The resulting excess claim fee has been calculated as shown below:

	After Amendment		Highest No. Previously Paid For						
All Claims	33	-	32	=	1	X	$52.00	=	$52.00
Independent	5	-	4	=	1	X	$220.00	=	$220.00
					TOTAL			=	**$272.00**

The statutory fee of $272.00 is being remitted. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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(54) Title: SUSTAINED DRUG-RELASE PARTICLES AND PROCESS FOR PRODUCING THE SAME

(54) 発明の名称: 薬物徐放性粒子及びその製法

(57) Abstract: It is intended to provide sustained theophylline-release particles that are sustained theophylline-release particles comprising a polyglycerol fatty acid ester as a matrix base, having a uniform cored particle structure, being able to effectively masking the unpleasant taste of the drug and having excellent properties of controlling the release (elution) of the drug and a high storage stability. More specifically speaking, a process for producing sustained theophylline-release particles characterized by comprising heating a matrix base containing a polyglycerol fatty acid ester, theophylline and ethyl cellulose to give a liquid mixture, spray-cooling the liquid mixture to give spherical cored particles having an average particle size of 250 μm or less and then melt-coating the cored particles with a fine powder, etc.

(57) 要約: 本発明は、ポリグリセリン脂肪酸エステルをマトリックス基剤としたテオフィリン徐放性粒子であって、均質な核粒子構造を有し、効果的に薬物の不快な味をマスキングすることができ、優れた薬物の放出（溶出）制御性及び優れた保存安定性を有するテオフィリン徐放性粒子を提供する。具体的には、ポリグリセリン脂肪酸エステルを含むマトリックス基剤、テオフィリン及びエチルセルロースを加熱して液状混合物とし、該液状混合物を噴霧冷却して平均粒子径250μm以下の球形の核粒子とし、該核粒子に微粉末を溶融コーティングすることを特徴とするテオフィリン徐放性粒子の製法等を提供する。

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しくは1～15μm程度、より好ましくは1～10μm程度の範囲から選択される。

また、核粒子と微粉末との混合割合は、目的とする薬物の溶出速度、核粒子の粒子径及び目的とする徐放性製剤の粒子径等に応じて決定すればよく、微粉末の使用量は、通常、核粒子100重量部に対して5～50重量部程度、好ましくは10～50重量部程度，より好ましくは10～45重量部程度であればよい。

溶融コーティングは、公知の方法に従い実施できる。例えば、上記で得られた核粒子に微粉末を混合し、撹拌下で加熱すればよい。加熱温度は、マトリックス基剤の融点（T_m）又は軟化点（T_s）付近、即ち；T付近まで加熱する。T付近とは、（T－15）℃～T℃、好ましくは（T－10）℃～T℃の範囲の温度であればよい。例えば、ポリグリセリン脂肪酸エステルとグリセリン脂肪酸エステルとからなるマトリックス基剤の場合、40～90℃程度、好ましくは45～80℃程度の範囲である。なお、溶融コーティング時間は、製造スケールによっても異なるが、通常5分～6時間程度であればよい。

本発明における核粒子への微粉末の溶融コーティングは、撹拌下（撹拌造粒法）、又は流動下（流動層造粒法）のいずれでもよい。撹拌下で行う場合は通常、公知の撹拌造粒装置を用い、流動下で行う場合は通常、公知の流動層造粒装置が用いられる。特に、撹拌下で溶融コーティングするのが好ましい。

ところで、流動式において核粒子を融点付近にまで加熱するためには融点以上の熱風を必要とし、流動層装置（壁面、下部メッシュ等）の温度が高いために核粒子が装置に付着溶融して凝集するため、収率が悪く，さらに徐放化を目的として粉体を核粒子に緻密に完全に付着することは実際困難となる場合がある。これに対し、撹拌式を採用すると、撹拌装置の容器温度（ジャケット温度）を目的とする核粒子の製品温度とほぼ同じ温度で制御することができ、また、ジャケット内に冷水を導入することにより装置全体を急速に冷却することも可能である。そのため核粒子の異常な加熱は発生し難く、壁面への溶融付着による凝集を完全に防ぐことが可能となる。

溶融コーティングで得られる粒子は球形であり、その平均粒子径は、通常、450μm以下、好ましくは400μm以下、より好ましくは30～400μm程